Medical Policy

Healthcare Services Department

Policy Name	Policy Number	Scope
Brentuximab vedotin (Adcetris®)	MP-RX-FP-01-23	☒ MMM MA ☒ MMM Multihealth

Service Category

☐ Anesthesia
☐ Surgery
☐ Radiology Procedures
☐ Pathology and Laboratory Procedures
☐ Medicine Services and Procedures
☐ Evaluation and Management Services
☐ DME/Prosthetics or Supplies
☒ Part B Drug

Service Description

This document addresses the use Brentuximab vedotin (Adcetris®) approved by the Food and Drug Administration (FDA) for the treatment of for certain patients with Hodgkin lymphoma (HL) and non-Hodgkin lymphoma.

Background Information

Adcetris is a monoclonal antibody-drug conjugate (ADC) that consists of a chimeric IgG1 directed antibody against CD30 and a small molecule, monomethyl auristatin E (MMAE), a microtubule- disrupting agent. The anticancer activity is due to the binding of the ADC to CD30-expressing cells causing disruption of the microtubule network leading to cell death. Adcetris is FDA approved for certain patients with Hodgkin lymphoma (HL) and non-Hodgkin lymphoma. The National Comprehensive Cancer Network (NCCN) provides additional recommendations with a category 2A level of evidence for the use of Adcetris.

Hodgkin Lymphoma (HL)

Adcetris was FDA approved in 2018 for previously untreated stage III or IV classical HL (cHL), in combination with chemotherapy. This FDA indication was updated later to read "in combination with doxorubicin, vinblastine, and dacarbazine". NCCN gives additional combination options for older adults with untreated HL, including sequential therapy or in combination with dacarbazine. It is also FDA approved for pediatric individuals 2 years of age and older with previously untreated high risk cHL, in combination with doxorubicin, vincristine, etoposide, prednisone, and cyclophosphamide. For relapsed HL, Adcetris is approved as a single agent after failure of autologous hematopoietic stem cell transplantation (auto-HSCT) or after failure of at least two prior multi-agent chemotherapy regimens when individuals were ineligible for transplant. In the relapsed setting, NCCN recommends Adcetris alone or in combination with bendamustine or nivolumab, and regardless of individual's eligibility for transplant. It is also approved as post-auto-HSCT consolidation therapy for those at high risk of relapse or progression. The clinical trial supporting this indication defined high risk as: primary refractory HL (failure to achieve complete remission, as determined by investigator), relapsed HL with an initial remission duration of less than 12 months, or extranodal involvement at the start of pre-transplantation salvage chemotherapy. NCCN recommends as maintenance therapy for 1 year if brentuximab naïve and Deauville score less than 5.

Non-Hodgkin Lymphoma (NHL)

NHLs are a broad and diverse group of malignancies affecting both B- and T-lymphocytes. Adcetris is mostly used for T-Cell Lymphomas. These can broadly be classified as cutaneous or non-cutaneous. Cutaneous T-cell

Policy Name	Policy Number	Scope
Brentuximab vedotin (Adcetris®)	MP-RX-FP-01-23	☒ MMM MA ☒ MMM Multihealth

lymphomas include mycosis fungoides (MF) and sezary syndrome (SS), lymphomatoid papulosis (LyP), and the cutaneous form of anaplastic large cell lymphoma (ALCL), known as primary cutaneous ALCL. "Non-cutaneous" T-cell lymphomas are diverse and NCCN divides the treatment algorithms into certain types such as peripheral t-cell lymphoma (PTCL), Adult T-cell leukemia/lymphoma (ATLL), breast implant-associated ALCL, extranodal NK/T-Cell lymphoma, nasal type (NKTL), and hepatosplenic T-Cell Lymphoma (HSTCL). Subtypes of PTCLs include but are not limited to PTCL-NOS (not-otherwise-specified), systemic ALCL, and angioimmunoblastic t-cell lymphoma.

Adcetris is FDA approved for relapsed primary cutaneous ALCL and CD30 expressing MF. NCCN recommends it also as first-line treatment of primary cutaneous ALCL and MF/SS when there is advanced disease presentation (which would disease that is stage IIB or higher, large cell transformation, extensive skin involvement, higher skin disease burden, primarily plaque disease, blood involvement, or inadequate response to skin-directed therapy). NCCN also recommends Adcetris for relapsed/refractory LyP with extensive lesions. Adcetris is also FDA approved to treat relapsed systemic ALCL after failure of at least one prior multi-agent chemotherapy regimen. In the area of relapsed disease, NCCN also recommends Adcetris for PTCL, angioimmunoblastic t-cell lymphoma, NKTL, HTL, and breast implant-associated ALCL. NCCN also recommends Adcetris as adjuvant therapy for breast implant-associated ALCL.

Adcetris is also FDA approved in combination cyclophosphamide, doxorubicin, and prednisone (CHP) for previously untreated CD30 expressing PTCL and systemic ALCL (which is a type of PTCL) based on the results of the ECHELON-2 study (Horwitz 2018). Study inclusion criteria states "newly diagnosed CD30+ mature T-cell lymphomas". NCCN additionally recommends this front-line regimen for patients with ATLL and the following types of PTCL: angioimmunoblastic t-cell lymphoma, enteropathy-associated T-cell lymphoma, monomorphic epitheliotropic intestinal T-cell lymphoma, nodal peripheral T-cell lymphoma with TFH phenotype, follicular T-cell lymphoma. NCCN also recommends Adcetris as secondary treatment for ATLL and for relapsed or refractory Primary Mediastinal Large B-Cell Lymphoma in combination with nivolumab.

Adcetris (brentuximab vedotin) has a black box warning for John Cunningham (JC) virus infection resulting in progressive multifocal leukoencephalopathy (PML). Fatal cases of JC virus infection resulting in PML have been reported in individuals receiving Adcetris.

Definitions and Measures

- Adjuvant therapy: Treatment given after the primary treatment to increase the chances of a cure; may include chemotherapy, radiation, hormone or biological therapy.
- Autologous stem cells: Stem cells harvested from the individual's own bone marrow or peripheral blood.
- Consolidation: Repetitive cycles of treatment during the immediate post-remission period; used especially for leukemia; also known as intensification therapy.
- Deauville Score: 5-point rating scale used in staging and response of HL and NHL; visual assessment of F-fluorodeoxyglucose (FDG) uptake in the involved sites. Score of 5 indicates markedly higher uptake initially involved site and/or new lesions.
- High-dose or myeloablative chemotherapy (HDC): The administration of cytotoxic agents using doses several times greater than the standard therapeutic dose.

Policy Name	Policy Number	Scope
Brentuximab vedotin (Adcetris®)	MP-RX-FP-01-23	☒ MMM MA ☒ MMM Multihealth

- Line of Therapy:
    - First-line therapy: The first or primary treatment for the diagnosis, which may include surgery, chemotherapy, radiation therapy or a combination of these therapies.
    - Second-line therapy: Treatment given when initial treatment (first-line therapy) is not effective or there is disease progression.
- Maintenance therapy: Designed to maintain a condition to prevent a relapse.
- Mycosis fungoides: A sub-type of cutaneous T-cell lymphoma in which tumor cells invade the skin causing reddening (erythroderma) and/or plaques. There may also be involvement of lymph nodes, blood, and internal organs.
- One line of therapy: Single line of therapy.
- Refractory Disease: Illness or disease that does not respond to treatment.
- Relapse or recurrence: After a period of improvement, during which time a disease (for example, cancer) could not be detected, the return of signs and symptoms of illness or disease. For cancer, it may come back to the same place as the original (primary) tumor or to another place in the body.
- Sézary Syndrome: A sub-type of cutaneous T-cell lymphoma characterized by itching and redness with T cell leukemia whose cells clonally match those invading the skin. Sézary Syndrome has historically been more difficult to treat than mycosis fungoides.

Approved Indications

FDA-approved indication
Adult patients with previously untreated Stage III or IV classical Hodgkin lymphoma
Pediatric patients with previously untreated high risk classical Hodgkin lymphoma
Adult patients with classical Hodgkin lymphoma consolidation
Adult patients with relapsed classical Hodgkin lymphoma
Adult patients with previously untreated systemic ALCL or other CD30-expressing peripheral T-cell lymphomas
Adult patients with relapsed Systemic ALCL
Adult patients with relapsed primary cutaneous ALCL or CD30-expressing mycosis fungoides

Other Uses

See Background Section above.

Policy Name	Policy Number	Scope
Brentuximab vedotin (Adcetris®)	MP-RX-FP-01-23	☒ MMM MA ☒ MMM Multihealth

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

HCPCS	Description
J9042	Injection, brentuximab vedotin, 1 mg [Adcetris]

ICD-10	Description
C81.00-C81.99	Hodgkin lymphoma
C84.00-C84.19	Mycosis fungoides, Sézary disease C84.40-C84.49
C84.60-C84.69	Anaplastic large cell lymphoma, ALK-positive C84.70-C84.79
C85.20-C85.29	Mediastinal (thymic) large B-cell lymphoma
C84.00-C84.19	Mycosis fungoides, Sézary disease C84.40-C84.49
C84.60-C84.69	Anaplastic large cell lymphoma, ALK-positive C84.70-C84.79
C85.20-C85.29	Mediastinal (thymic) large B-cell lymphoma
C86.1	Hepatosplenic T-cell lymphoma
C86.2	Enteropathy-type (intestinal) T-cell lymphoma
C86.5	Angioimmunoblastic T-cell lymphoma
C86.6	Primary cutaneous CD30-positive T-cell proliferations
C91.50	Adult T-cell lymphoma/leukemia (HTLV-1-associated) not having achieved remission
C91.51	Adult T-cell lymphoma/leukemia (HTLV-1-associated), in remission
C91.52	Adult T-cell lymphoma/leukemia (HTLV-1-associated), in relapse
Z85.71	Personal history of Hodgkin lymphoma
Z85.72	Personal history of non-Hodgkin lymphomas

Policy Name	Policy Number	Scope
Brentuximab vedotin (Adcetris®)	MP-RX-FP-01-23	☒ MMM MA ☒ MMM Multihealth

Medical Necessity Guidelines

When a drug is being reviewed for coverage under a member's medical benefit plan or is otherwise subject to clinical review (including prior authorization), the following criteria will be used to determine whether the drug meets any applicable medical necessity requirements for the intended/prescribed purpose.

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

Brentuximab vedotin (Adcetris®)

A. Criteria For Initial Approval

i. Individual has a diagnosis of Hodgkin Lymphoma (HL); **AND**

ii. Individual is using for one of the following:

A. Previously untreated stage III or IV classical HL, in combination with doxorubicin, vinblastine, and dacarbazine; **OR**

B. Previously untreated classical HL in older adults (≥60 years), as sequential therapy with doxorubicin, vinblastine, and dacarbazine, or in combination with dacarbazine (NCCN 2A); **OR**

C. Previously untreated high risk classical HL, in combination with doxorubicin, vincristine, etoposide, prednisone, and cyclophosphamide; **OR**

D. Relapsed or refractory disease in a single line of therapy as a single agent or in combination with bendamustine or nivolumab or pembrolizumab (Label, NCCN 2A); **OR**

E. Relapsed or refractory disease as second or subsequent line of therapy in combination with ifosfamide, carboplatin, etoposide; **OR**

F. As consolidation therapy after an autologous stem cell transplantation for individuals at high risk of relapse or progression, defined as individuals with any of the following:

1. Primary refractory HL; **OR**
2. Relapsed HL with an initial remission duration of less than 12 months; **OR**
3. Extranodal involvement at the start of pre-transplantation salvage chemotherapy;

OR

G. As maintenance therapy for 1 year following high-dose therapy and autologous stem cell rescue for relapsed or refractory disease in those who are brentuximab vedotin naïve and have a Deauville score of less than 5 (NCCN 2A);

OR

iii. Individual has a diagnosis of CD30+ Non-Hodgkin Lymphoma; **AND**

iv. Individual is using for one of the following:

A. Cutaneous anaplastic large cell lymphoma; **OR**

B. Cutaneous T-cell lymphoma, including mycosis fungoides/Sézary syndrome, for the following:

1. Relapsed or refractory or persistent disease; **OR**

2. As first-line therapy for advanced disease presentation (for example, large cell transformation, extensive skin involvement, higher skin disease burden, primarily plaque disease, blood involvement, inadequate response to skin-directed therapy, or state IIB or higher) (NCCN 2A);

OR

C. Relapsed or refractory lymphomatoid papulosis with extensive cutaneous lesions (NCCN 2A);

OR

D. In combination with cyclophosphamide, doxorubicin, and prednisone, for previously untreated:
   1. Peripheral T-cell lymphoma (including systemic anaplastic large cell lymphoma, angioimmunoblastic t-cell lymphoma, enteropathy-associated T-cell lymphoma, monomorphic epitheliotropic intestinal T-cell lymphoma, nodal peripheral T-cell lymphoma with TFH phenotype, follicular T-cell lymphoma) (Label, NCCN 2A);

OR

E. Adult T-cell leukemia/lymphoma (NCCN 2A);

OR

F. One of the following T-cell lymphomas, as treatment for relapsed or refractory disease:
   1. Systemic anaplastic large cell lymphoma (Label);
   2. Extranodal NK/T-Cell lymphomas (NCCN 2A);
   3. Hepatosplenic T-Cell lymphoma (NCCN 2A);
   4. Breast implant-associated anaplastic large cell lymphoma (NCCN 2A);
   5. Peripheral T-cell lymphoma (NCCN 2A);
   6. Angioimmunoblastic T-cell lymphoma (NCCN 2A);

OR

G. As an adjuvant systemic therapy for breast implant-associated anaplastic large cell lymphoma for either of the following (NCCN 2A):
   1. Residual, localized disease (confined to capsule/implant/breast) following partial excision or capsulectomy;

   OR

   2. Extended disease (stage II-IV);

OR

H. Individual has relapsed or refractory Primary Mediastinal Large B-Cell Lymphoma; **AND**
   1. Individual is using in combination with nivolumab (NCCN 2A);

OR

I. One of the following B-Cell Lymphomas (NCCN 2A):
   1. Relapsed or refractory Diffuse Large B-Cell Lymphomas (DLBCL) (NCCN 2A); **OR**
   2. Post-Transplant lymphoproliferative disorders; **OR**
   3. High-grade B-Cell Lymphomas

OR

J. Individual has a diagnosis of pediatric Hodgkin Lymphoma; **AND**

K. Individual is using for one of the following:

Policy Name	Policy Number	Scope
Brentuximab vedotin (Adcetris®)	MP-RX-FP-01-23	☒ MMM MA ☒ MMM Multihealth

1. Primary or subsequent treatment for high-risk disease (high risk defined as progressive disease, refractory disease, or relapse within 1 year of original diagnosis) (NCCN 1, 2A); **OR**
2. Treatment therapy for heavily pretreated disease or decrease in cardiac function (NCCN 2A) in combination with bendamustine or nivolumab or gemcitabine.

B. Criteria For Continuation of Therapy

i. MMM considers continuation of Brentuximab vedotin (Adcetris®) therapy medically necessary in members requesting reauthorization for an indication listed in Section A above (Criteria for Initial Approval) when there is no evidence of unacceptable toxicity or disease progression while on the current regimen, and the recommended duration of therapy has not been exceeded. The following information should be submitted for reauthorization:

A. A current oncology note documenting the patient's response to treatment showing no progression of disease.

B. Current imaging studies and other objective measures, as appropriate, showing no progression of disease when compared with previous results (every six months).

Indication	Maximum duration of therapy
Adult patients with previously untreated Stage III or IV classical Hodgkin lymphoma	Every 2 weeks for maximum of 12 doses, disease progression, or unacceptable toxicity
Pediatric patients with previously untreated high risk classical Hodgkin lymphoma	Administer every 3 weeks with each cycle of chemotherapy for a maximum of 5 doses
Adult patients with classical Hodgkin lymphoma consolidation	Every 3 weeks for a maximum of 16 cycles, disease progression, or unacceptable toxicity.
Adult patients with relapsed classical Hodgkin lymphoma	Every 3 weeks until disease progression or unacceptable toxicity
Adult patients with previously untreated systemic ALCL or other CD30-expressing peripheral T-cell lymphomas	Administer every 3 weeks with each cycle of chemotherapy for 6 to 8 doses.
Adult patients with relapsed Systemic ALCL	Every 3 weeks until disease progression or unacceptable toxicity
Adult patients with relapsed primary cutaneous ALCL or CD30-expressing mycosis fungoides	Every 3 weeks until a maximum of 16 cycles, disease progression, or unacceptable toxicity.

Policy Name	Policy Number	Scope
Brentuximab vedotin (Adcetris®)	MP-RX-FP-01-23	☒ MMM MA ☒ MMM Multihealth

C. Authorization Duration

i. Initial Approval Duration: Depending on the diagnosis, it will be approved per cycle or as requested, for up to 6-month (for the maximum duration of treatment as described in the product labeling information or approved compendia).

ii. Reauthorization Approval Duration: Depending on the diagnosis, it will be approved per cycle or as requested, for up to 6-month (for the maximum duration of treatment as described in the product labeling information or approved compendia).

D. **Conditions Not Covered**

Any other use is considered experimental, investigational, or unproven, including the following (this list may not be all inclusive):

i. Requests for Adcetris (brentuximab vedotin) may not be approved when the above criteria are not met and for all other indications.

Limits or Restrictions

A. Quantity Limitations

Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines. The chart below includes dosing recommendations as per the FDA-approved prescribing information.

FDA-approved indication	Recommended Dose*	Maximum dose
Adult patients with previously untreated Stage III or IV classical Hodgkin lymphoma	1.2 mg/kg every 2 weeks in combination with chemotherapy	120 mg
Pediatric patients with previously untreated high risk classical Hodgkin lymphoma	1.8 mg/kg every 3 weeks in combination with chemotherapy	180 mg
Adult patients with classical Hodgkin lymphoma consolidation	1.8 mg/kg every 3 weeks	180 mg
Adult patients with relapsed classical Hodgkin lymphoma	1.8 mg/kg every 3 weeks	180 mg
Adult patients with previously untreated systemic ALCL or other CD30-expressing peripheral T-cell lymphomas	1.8 mg/kg every 3 weeks in combination with chemotherapy	180 mg
Adult patients with relapsed Systemic ALCL	1.8 mg/kg every 3 weeks	180 mg
Adult patients with relapsed primary cutaneous ALCL or CD30-expressing mycosis fungoides	1.8 mg/kg every 3 weeks	180 mg

Policy Name	Policy Number	Scope
Brentuximab vedotin (Adcetris®)	MP-RX-FP-01-23	☒ MMM MA ☒ MMM Multihealth

Exceptions
None

*The dose for patients weighing greater than 100 kg should be calculated based on a weight of 100 kg.

Reference Information

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5. Cole PD, Mauz-Korholz C, Mascarin M, et al. Nivolumab and brentuximab vedotin (BV)-based, response-adapted treatment in children, adolescents, and young adults (CAYA) with standard-risk relapsed/refractory classical Hodgkin Lymphoma (R/R cHL): Primary analysis. J Clin Oncol 2020;38:8013 [Abstract].
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8. Herrera AF, Moskowitz AJ, Bartlett NL, et al. Interim results of brentuximab vedotin in combination with nivolumab in patients with relapsed or refractory Hodgkin lymphoma. Blood 2018; 131: 1183-1194. [NCT02572167].
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10. Lynch RC, Cassaday RD, Smith SD, et al. Dose-dense brentuximab vedotin plus ifosfamide, carboplatin, and etoposide for second-line treatment of relapsed or refractory classical Hodgkin lymphoma: a single centre, phase 1/2 study. Lancet Haematol. 2021;8(8):e562-e571. doi:10.1016/S2352-3026(21)00170-8. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8457616/. Accessed April 3, 2023.
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https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9098158/. Accessed March 29, 2023

12. NCCN Clinical Practice Guidelines in Oncology. © 2022 National Comprehensive Cancer Network, Inc. For additional information visit the NCCN website: http://www.nccn.org/index.asp. Accessed March 2023.
    a. B-Cell Lymphomas. V2.2023. Revised February 8, 2023.

Policy Name	Policy Number	Scope
Brentuximab vedotin (Adcetris®)	MP-RX-FP-01-23	☒ MMM MA ☒ MMM Multihealth

b. Hodgkin Lymphoma. V2.2023. Revised November 8, 2022.
c. Pediatric Aggressive Mature B-Cell Lymphomas. V1.2023. Revised April 4, 2023.
d. Pediatric Hodgkin lymphoma. V2.2023. Revised March 9, 2023.
e. Primary Cutaneous Lymphomas. V1.2023. Revised January 5, 2023.
f. T-Cell Lymphomas. V1.2023. Revised January 5, 2023.

Federal and state laws or requirements, contract language, and Plan utilization management programs or polices may take precedence over the application of this clinical criteria.

Policy History

Revision Type	Summary of Changes	P&T Approval Date	MPCC Approval Date
Policy Inception	Elevance Health's Medical Policy adoption.	N/A	11/30/2023

Revised: 10/12/2023